REMARKS

Entry of the amendment is respectfully requested since it would lessen the issues on appeal. Further, Applicants respectfully request that the finality of the rejection be withdrawn in light of an apparently new ground of rejection. It appears that the Examiner is relying on references cited and relied upon in the text of the rejection but not included in his statement of the second Obviousness rejection.

Claims 1-4, 6, 10, 14, 16, 17 and 20-21 will be before the Examiner upon entry of the amendment. Claims 7-9, 11, 18 and 19 remain withdrawn from consideration by the Examiner as directed to a non-elected invention(s). Claim 5 is canceled. The canceled claim appears to recite inherent characteristics of one or more of the named active ingredients recited in claim 1. Claim 1 has been amended to more clearly indicate that the subject has a malady which is treated by the active ingredient and that the complement activation inhibitor is administered in an effective amount to treat the immediate hypersensitivity reaction caused by the polyethoxylated oil or a derivatized polyethoxylated oil. The new claims 20 and 21 recite disclosed and exemplified complement inhibitors, respectively.

Claims 1-6, 10, 14 and 16-17 under 35 U.S.C. §103(a) as being unpatentable over Ko et al. .(US 5,851,528) or in combination with De Lacharriere et al. (U.S. Patent No. 5,744,156). Applicants respectfully traverse.

Claim 1 has been amended to make clear that a drug, complement inhibitor and polyethoxylated oil or a derivatized polyethoxylated oil carrier is administered to a subject having a malady for which the active ingredient is a treatment and the complement inhibitor suppresses or alleviates the immediate hypersensitivity reaction caused by the carrier.

None of the references teach either the cause of the immediate hypersensitivity reaction as being polyethoxylated oil or a derivatized polyethoxylated oil carrier nor its solution. The past solution has been to remove the polyethoxylated oil from the formulation. (See the previously submitted Attachment and "Supplemental Response").

Ko et al. teach chimeric molecules composed of a first and second polypeptide. Both peptides are inhibitors of complement activation. The first and second peptides of the chimeric molecule may be the same or different. MCP-DAF ("CAB-2") is exemplified. The chimeric molecule inhibitor is taught to reduce inflammation. See Example 8. Suggested treatable conditions listed include those associated with ischemia-reperfusion, crash injury, burns, ARDS, autoimmune disorders, etc.. Table 1 also suggests potential clinical targets of the protein chimeras, i.e. targets to try. [1] Table 1 mentions "Drug Allergy". There is no detailed description for the term in terms of mechanism or type. (Here, we are concerned with an immediate hypersensitivity reaction caused by a carrier material, a nondrug.)

There is no formulation suggested in Ko et al. where an active ingredient is combined with a complement inhibitor, which inhibitor is included to suppress an immediate hypersensitivity reaction. Immediate hypersensitivity reaction is not mentioned as a target in Ko et al. Neither polyethoxylated oil nor a derivatized polyethoxylated oil is mentioned as a causative agent for an immediate hypersensitivity reaction.

De Lacharriere et al. does not remedy the deficiencies of Ko et al. in terms of identifying the cause of an immediate hypersensitivity reaction caused by a specific type of carrier nor in suggesting a solution to the problem.

De Lacharriere teaches the use of a substance P antagonist for the preparation of a pharmaceutical composition for treating skin reddening of a neurological origin. There is no mention of an immediate hypersensitivity reaction associated with complement activation by amphiphilic molecules nor its treatment in the manner claimed. The exemplified formulations

[1] The art of pathological conditions associated with complement activation in the field of complement prior to the instant disclosed invention are described in previously submitted Table A. Applicants consulted 44 reviews, research, or textbook articles in the field. Many of these reviews, both before and after 1998 (the Ko, et al patent issued on 22 Dec 98), gave comprehensive listing of pathological conditions associated with complement activation. Each of the pathological conditions mentioned by Ko, et al are included. The first mention of immediate non-IgE hypersensitivity reactions mediated by complement was published by Applicants in Feb, 1998.

for treating skin reddening of a neurological origin do not suggest the formulation administered in the manner claimed.

It is respectfully submitted that the teachings of the art relied upon whether taken alone or together do not suggest the invention as now claimed. There is no suggestion of the combination of the activity of the claimed active ingredient, carrier and complement inhibitor. Withdrawal of the rejection is respectfully requested.

Claims 1-6, 10, 14 and 16-17 under 35 U.S.C. §103(a) as being unpatentable over Ko (5,851,528) by itself or in combination with De Lacharriere (US 5,744, 156), in further combination with applicant's statement of prior art. Applicants respectfully traverse.

The Examiner admits that neither Ko et al. nor De Lacharriere et al teach the use of cremophor as a drug or carrier. The Examiner further admits that neither of these references teach that cremophors or liposomes cause compliment activation. The Examiner points to pages 5 and 6 of the instant specification where various references are cited which are characterized as showing that cremophor and liposomes cause compliment activation. (The Examiner makes specific reference to Michaud at page 1402 (col.2) cremophor EL causes hypersensitivity reactions though on rare occasions.) The Examiner then urges that 1) it would be obvious to use Kook's (Ko et al. 's ?) inhibitors for chremophor induce side effects and that 2) one would expect similar results irrespective of what causes the complement activation. (No reference is cited in support of this proposition.)

Applicants submit that the rejection as stated relies on hindsight and is based on "obvious to try" rather than statutory obviousness.

The "teachings" relied upon in the passage on pages 5 and 6 relied upon by the Examiner is taken out of context. The "Background" section taken as a whole suggests that there was uncertainty at the time of the invention as to the causative factor, e.g. drug, carrier, mechanism involved and response type.

The "Background" section begins with a statement that one problem associated with the clinical use of paclitaxel has been the frequent presence of acute hypersensitivity re actions. Further on in the section (p. 3), there is a clear indication that the mechanism of induction of hypersensitivity reactions in response to paclitexel administration had not yet been elucidated and that current research at that time in the area of the endeavor had generated an ongoing debate on the phenomenon. In particular, there was at the time no consensus in the literature regarding two questions: 1) whether the reaction is due to paclitaxel or to the vehicle, cremophor EL, and 2) whether the phenomena represents an immunoglobulin e(IgE)-mediated classical type 1 allergic reaction, or did it arises as a consequence of direct drug effect on mast cells and/or basophils, causing massive histamine release.

It is not clear from the record why the Michaud reference specifically identified by the Examiner is to be considered to the exclusion of the Essayan et al. (1996) reference, which contradicted the view as to Cremophor EL as the causative factor and pointed to paclitaxel as the offender. The "Background" section provides a balanced view of the art to which Applicants' invention is directed. At the end of the background section, the conclusion is reached that there is still a need to determine the mechanism behind the hypersensitivity reactions described above. This section suggests there was still uncertainty and a degree of unpredictability at the time of the invention. It was not reasonably certain that if one administered a complement inhibiter, one would have reasonably expected that the hypersensitivity reaction under consideration here would have been suppressed. It was not even certain that Cremophor EL was the cause.

The examiners reliance on the teaching of the Michaud reference appears to have been aided by the teaching of the application as a whole including the successful outcome achieved by Applicants' experimentation. It is not clear from the record why the ordinary skilled artisan would select the Michaud teaching in preference to the contrary teachings of the Essayan et al. (1966) reference, also cited in the specification. The ordinary skilled artisan would have considered the whole picture. Accordingly, it would appear that one of ordinary skill would not be as certain of the outcome at the outset and may have even considered the outcome achieved by Applicants as unexpected. Further, the Examiner does not make it clear why replacement of the carrier would not have been the solution.

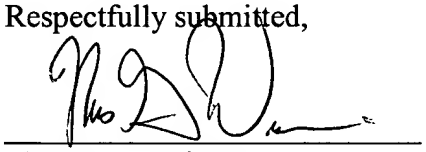
Presently, ignoring the Examiner's use of the specification to guide him to the selection of the teachings of Michaud rather than Essayan et al., it is respectfully submitted that the Examiner rationale in reaching the claimed invention is based on "obvious to try" rather than to statutory obviousness. Withdrawal of the rejection is respectfully requested on this ground alone.

Further, withdrawal of the rejection is further requested because it is based on teachings, which are incomplete to arrive at the invention as claimed. There is no teaching of co-administration of the active ingredient and the inhibitor by either Ko et al or De Lacharriere. There is no clear, unequivocal teaching of polyethoxylated oil or a derivatized polyethoxylated oil as the causative agent for the immediate hypersensitivity reaction addressed by the claimed method.

In view of the foregoing amendments and remarks, the application is believed to be in condition for allowance and a notice to that effect is respectfully requested.

Should the Examiner not agree that the Application to be in allowable condition or believe that a conference would be of value in expediting the prosecution of the Application, Applicants request that the Examiner telephone undersigned Counsel to discuss the case and afford Applicants an opportunity to submit any Supplemental Amendment that might advance prosecution and place the Application in allowable condition.

Respectfully submitted,



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